position alpha to the amine group. The differences relate to the biological and pharmacokinetic characteristics of the compounds, including their high affinity for the relevant receptor (the $\alpha 4\beta 2$ receptor), their ability to elicit functional response at the receptor, and their resistance to metabolic clearance. Accordingly, the Declaration demonstrated the superiority of pyridinyl compounds with an alpha methyl group (*i.e.*, alpha to the amine group) versus pyridinyl compounds without an alpha methyl group. The Office Action raised two issues, both of which are addressed herein.

The R alpha methyl isomer

The first issue raised was that the Declaration shows that the R alpha methyl isomer is about as active as the unsubstituted compound, and in the Examiner's view, this does not support a finding of unexpected/superior properties. It is believed that this ground of rejection does not apply to claims 24 and 26, as they are directed to the S alpha methyl isomers. With respect to claims 21-23, 25 and 27, Applicants respectfully disagree with the Examiner's position regarding the R alpha methyl isomer compounds.

Binding is one property, and metabolic clearance is another. The issue is not whether the alpha methyl compounds bind more tightly to the receptor than similar compounds that are not substituted with an alpha methyl group. The issue is that the compounds with alpha methyl substitution offer superior resistance to metabolic clearance and suitable binding to the relevant receptor.

Even if the alpha methyl compounds bind the relevant receptor with similar binding constants as the alpha CH_2-substituted compounds, the alpha methyl compounds have totally different metabolic properties, and have significantly improved *in vivo* half-lives. That feature is sufficient to demonstrate that the claimed compounds are non-obvious over prior art compounds that did not include alpha methyl substitution.

The previously submitted Declaration demonstrated that, in light of problems associated with the metabolism of N-methyl-4-(3-pyridinyl)-3-buten-1 amines, an effort was made to identify compounds that possessed both good binding/functional characteristics and good

pharmacokinetic profiles. During the course of the research, which involved forming a plurality of compounds with substituents at varying positions, the results (and the isolation of metabolites) indicated that the problem might involve monoamine oxidase activity at the secondary amine side chain. After identifying the problem, the next step was to provide a (non-obvious) solution to the problem. Many proposed solutions to this problem overcame the metabolic issue, but failed to provide adequate binding to the relevant receptor. However, one solution not only overcame the problem, but also retained the binding to the relevant receptor. This solution came in the form of providing an alpha alkyl (in this case, alpha methyl) substituent.

The alpha methyl compounds showed improved metabolic characteristics and retained binding at the $\alpha 4\beta 2$ receptor. The unexpected result is that the compounds have an improved overall combination of biological and pharmacokinetic characteristics (high affinity for the receptor, ability to elicit functional response at the receptor and resistance to metabolic clearance). These characteristics make the claimed α-methyl compounds significantly better drug candidates than the corresponding unsubstituted analogs. The claimed compounds are an example of such compounds, and are therefore non-obvious in view of Caldwell.

Accordingly, Applicants respectfully request that the Examiner withdraw this ground of rejection.

Trans (E) and Cis (Z) isomers

The Declaration showed examples of trans compounds, both with and without the alpha methyl substituent, and compared the metabolic activity of these compounds. The Declaration did not include examples of cis compounds. The second issue raised in the Office Action was whether the claimed compounds that are in the form of cis-isomers also benefit from the claimed superior properties. It is believed that this ground of rejection does not apply to claims 22, 26 and 27, as they are directed to trans compounds (which, as amended herein, are independent claims). With respect to claims 21 and 23-25, Applicants respectfully assert that the cis compounds do benefit from the claimed superior properties.

Applicants have prepared numerous cis compounds, and note that they do bind the relevant receptor with suitable binding affinity, although perhaps not with the same high affinity as the corresponding trans-isomers. The issue is whether the cis-isomers also benefit from the superior resistance to metabolic clearance.

The effect of the alpha methyl substitution is believed to involve steric hindrance to amine oxidases that otherwise deaminate the amine group at the adjacent position. This effect would not be expected to be adversely effected by a cis/trans orientation of the heteroaryl ring at a position far removed from the relevant carbon (*i.e.*, the carbon to which both the amine and methyl group are attached). Clearly, the alpha methyl group provides no less steric hindrance to the directly adjacent amine group when a pyridine ring is cis or trans at a position three carbons away from the alpha position. No sound scientific reason has been provided to doubt that trans alpha methyl pyridines would have improved metabolic clearance and cis alpha methyl pyridines would not. Accordingly, the Examiner is respectfully requested to withdraw this ground of rejection.

Provisional Non-statutory Double Patenting Rejections

Claims 21-27 stand provisionally rejected for non-statutory type double patenting over co-pending U.S. applications 08/631,761 and 09/642,351. A terminal disclaimer is enclosed, thus obviating the rejections. This terminal disclaimer supercedes and replaces the previously filed terminal disclaimer.

Conclusion

For at least the reasons set forth herein, Applicants submit all of pending claims 21-29 are in condition for allowance. Prompt consideration and action in the form of a Notice of Allowance is thus respectfully requested. However, should the arguments presented above with respect to the R isomers and/or cis isomers not be considered persuasive, claims to the S and/or trans isomers should otherwise be allowable. Accordingly, even if some issues remain following

consideration of this amendment, Applicants respectfully request indication of allowance of such claims.

Should the Examiner have any questions, he is invited to contact Applicants' undersigned representative at the telephone number below.

Respectfully submitted,

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Docket No.: T103 1300.2

Appendix – Claims as Amended

22. (Amended) [The] A compound [according to Claim 21, wherein the compound has a trans (E) form] selected from the group consisting of (2S)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine and (2R)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine.

25. (Amended) The compound according to Claim 21, wherein the compound has [ha] an (R) configuration.

26. (Amended) [The] A compound [according to Claim 21, wherein the compound is] denoted (2S)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine.

27. (Amended) [The] A compound [according to Claim 21, wherein the compound is] denoted (2R)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine.